

# NEW ZEALAND DATA SHEET

## 1. FENPAED ORAL SUSPENSION

Fenpaed oral suspension 100 mg/5 mL

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fenpaed 100 mg/5mL: Each 5 mL of oral suspension contains 100 mg of ibuprofen

### Excipients with known effect:

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral suspension.

FENPAED Oral Suspension is a white, strawberry flavoured suspension containing 100 mg ibuprofen per 5 mL

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Rheumatoid arthritis
- Osteoarthritis
- Juvenile rheumatoid arthritis
- Primary dysmenorrhoea
- Pyrexia

FENPAED is also indicated for the relief of acute and/or chronic pain states in which there is an inflammatory component.

### 4.2 Dose and method of administration

After assessing risk/benefit ratio in each individual patient, the lowest effective dose for the shortest duration should be used.

#### Adults Dose

Although Ibuprofen tablets are generally used for adults, when there are swallowing difficulties, FENPAED Oral Suspension can be used at an appropriate dosage:

The initial recommended dosage is 1200 - 1800 mg (60 – 90 mL) daily in divided doses. Some patients can be maintained on 600 - 1200 mg (30 mL – 60 mL) daily. In severe or acute conditions it can be advantageous to increase the dosage until the acute phase is brought under control, providing that the total daily dosage does not exceed 2400 mg (120 mL) in divided doses.

## **Maintenance dose**

In all indications the dose should be adjusted for each patient and the smallest dose that results in acceptable control of the symptoms employed. In general, patients with rheumatoid arthritis and osteoarthritis tend to require higher doses than patients with other conditions.

## **Special populations**

### **Elderly**

Elderly patients are more prone to adverse effects. Caution must be taken with dosage in this group and also in patients with renal impairment or impaired liver function.

### **Hepatic impairment**

Ibuprofen should be used with caution in patients with impaired liver function.

### **Renal impairment**

Ibuprofen should be used with caution in patients with impaired renal function.

### **Paediatric**

For infants and children a daily oral dose of 20 mg/kg body weight in divided doses. Up to 40 mg/kg body weight daily in divided doses may be recommended in cases of juvenile rheumatoid arthritis (Still's Disease).

In children weighing less than 30 kg, the total daily dose of FENPAED Oral Suspension should not exceed 500 mg.

Examples of typical daily doses are:

Six months - one year: Dose to be assessed by the physician.

1 - 5 years: Up to 5 mL given 3 to 4 times a day (total maximum daily dose 20 mL)

5 - 12 years: Up to 10 mL given 3 to 4 times a day (total maximum daily dose 40 mL)

## **4.3 Contraindications**

- Known hypersensitivity to ibuprofen or any of the inactive ingredients (see section 6.1).
- Hypersensitivity (e.g. asthma, rhinitis or urticaria) to aspirin or other nonsteroidal anti-inflammatory drugs.
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- History of ulcerative colitis, Crohn's disease, recurrent peptic ulceration or gastrointestinal hemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure (NYHA IV)
- Severe liver failure.
- Severe renal failure (glomerular filtration below 30 mL/min).
- Conditions involving an increased tendency or active bleeding.
- During the third trimester of pregnancy.

## **4.4 Special warnings and precautions for use**

### **General precautions**

Prolonged use of any painkillers may induce headaches, which must not be treated with increased doses of the painkillers, including ibuprofen. Through concomitant consumption of alcohol, NSAID-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased on use of NSAIDs.

### **Cardiovascular thrombotic events**

Clinical studies suggest that use of ibuprofen, particularly at a high dose (2400 mg/day) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen ( $\leq 1200$  mg/day) is associated with an increased risk of arterial thrombotic events.

Patients with uncontrolled hypertension, congestive heart failure (NYHA II-III), established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.

Careful consideration should also be exercised before initiating treatment in patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

### **Hypertension**

NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

### **Heart failure**

Fluid retention and oedema have been reported in association with ibuprofen, therefore, the medicine should be used with caution in patients with a history of heart failure or hypertension.

### **Gastrointestinal events**

Ibuprofen should be used with extreme caution, and at the lowest effective dose, in patients with a history of gastrointestinal haemorrhage or ulcer since their condition may be exacerbated. All NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy.

However, even short-term therapy is not without risk.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, as well as patients requiring concomitant low dose aspirin, or for other drugs likely to increase gastrointestinal risk.

The concomitant administration of ibuprofen and other NSAIDs, including cyclooxygenase-2 (Cox-2) selective inhibitors, should be avoided due to the increased risk of ulceration or bleeding.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately.

Doctors should warn patients about signs and symptoms of serious gastrointestinal toxicity.

Caution should be exercised in patients receiving concomitant medication which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or antiplatelet drugs such as aspirin.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

### **Severe skin reactions**

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) and Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) (see Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity. Ibuprofen should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

In exceptional cases, varicella can be at the origin of serious cutaneous and soft tissue infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of ibuprofen in case of varicella.

### **Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome**

DRESS syndrome has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS syndrome typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS syndrome may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

### **Infections and infestations**

Exacerbation of skin infection-related inflammations (e.g. development of necrotising fasciitis) coinciding with the use of NSAIDs has been described. If signs of an infection occur or get worse during use of Ibuprofen the patient is therefore recommended to go to a doctor without delay.

### **Respiratory disorders**

Caution is required if ibuprofen is administered to patients suffering from, or with a previous history of bronchial asthma, chronic rhinitis or allergic diseases since ibuprofen has been reported to cause bronchospasm, urticarial or angioedema in such patients.

### **Ophthalmological effects**

Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with ibuprofen should have an ophthalmological examination.

### **Impaired liver function or a history of liver disease**

Patients with impaired liver function or a history of liver disease who are on long term ibuprofen therapy should have hepatic function monitored at regular intervals. Ibuprofen has been reported to have a minor and transient effect on liver enzymes.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, though rare, have been reported with ibuprofen as with other NSAIDs. If abnormal liver tests persist or worsen, or if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), ibuprofen should be discontinued.

### **Impaired renal function**

Caution should be used when initiating treatment with ibuprofen in patients with considerable dehydration. There is a risk of renal impairment especially in dehydrated children and adolescents. The two major metabolites of ibuprofen are excreted mainly in the urine and impairment of renal function may result in their accumulation. The significance of this is unknown. NSAIDs have been reported to cause nephrotoxicity in various forms; interstitial nephritis, nephrotic syndrome and renal failure. In patients with renal, cardiac or hepatic impairment, those taking diuretics and ACE Inhibitors, and the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function.

The long-term concomitant intake of various analgesics further increases the risk. For patients with renal, hepatic or cardiac impairment, use the lowest effective dose, for the shortest possible duration and monitor renal function especially in long term treated patients.

### **Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics**

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

### **Aseptic meningitis**

Aseptic meningitis has been reported only rarely, usually but not always in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

### **Haematological monitoring**

Blood dyscrasias have been rarely reported. Patients on long term therapy with ibuprofen should have regular haematological monitoring.

### **Coagulation defects**

Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

### **Masking signs of infection**

As with other drugs of this class, ibuprofen may mask the usual signs of infection.

### **Withdrawal of concomitant steroid therapy**

In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

## **4.5 Interaction with other medicines and other forms of interaction**

### **Anticoagulants**

Care should be taken in patients treated with anti-coagulants, such as warfarin, due to an enhanced effect of anti-coagulants.

Concurrent use of NSAIDs and warfarin has been associated with severe sometimes fatal haemorrhage. The mechanism of this interaction is not known but may involve increased bleeding from NSAID-induced gastrointestinal ulceration or an additive effect of NSAID inhibition of platelet function with the anticoagulant effect of warfarin.

FENPAED should only be used in patients taking warfarin if absolutely necessary. Patients taking this combination must be closely monitored.

### **Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)**

Increased risk of gastrointestinal bleeding.

### **Aminoglycosides**

NSAIDs may decrease the excretion of aminoglycosides.

### **Lithium**

Ibuprofen has been shown to decrease the renal clearance and increase plasma concentrations of lithium.

Lithium plasma concentrations should be monitored in patients on concurrent ibuprofen therapy.

### **Cardiac glycosides**

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma

cardiac glycoside levels. Care should therefore be taken in patients treated with cardiac glycosides.

### **Cholestyramine**

The concomitant administration of ibuprofen and cholestyramine may reduce the absorption of ibuprofen in the gastrointestinal tract. However, the clinical significance is unknown.

### **Corticosteroids**

Increased risk of gastrointestinal ulceration or bleeding.

### **Herbal extracts**

Ginkgo biloba may potentiate the risk of bleeding with NSAIDs.

### **Other analgesics**

Avoid concomitant use of two or more NSAIDs, including aspirin and cyclooxygenase-2 (COX-2) selective inhibitors, because of the potential of increased adverse effects. Ibuprofen antagonizes the irreversible inhibition of platelet COX-1 induced by low dose aspirin. To reduce this effect, ibuprofen should be administered at least 8 hours before or 30 minutes after taking low dose aspirin.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 hours before, or within 30 minutes after immediate release aspirin (81 mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

### **Ciclosporin or tacrolimus**

Increased risk of nephrotoxicity when used with NSAIDs.

### **Methotrexate**

NSAIDs inhibit tubular secretion of methotrexate in animals. As a result, reduction of clearance of methotrexate may occur. Use of high doses of methotrexate concomitant with NSAIDs should be avoided. At low doses of methotrexate caution should be used if ibuprofen is administered concomitantly.

### **Mifepristone**

A decrease in the efficacy of the medicinal product can theoretically occur due to the antiprostaglandin properties of NSAIDs including acetylsalicylic acid. Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medicinal termination of pregnancy.

### **Quinolone antibiotics**

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing

convulsions.

### **Sulfonylureas**

NSAIDs may potentiate the effects of sulfonylurea medications. There have been rare reports of hypoglycemia in patients on sulfonylurea medications receiving ibuprofen.

### **Zidovudine**

Increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthroses and hematoma in HIV(+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

### **Others**

Ibuprofen like other NSAIDs can reduce the antihypertensive effect of ACE inhibitors, angiotensin II receptor antagonists and beta-blockers with possible loss of blood pressure control and can attenuate the natriuretic effects of diuretics. Diuretics can also increase the risk of nephrotoxicity of NSAIDs. The combined use of the three classes of drugs, diuretics, an ACE inhibiting drug (ACE inhibitor or angiotensin receptor antagonist) and an anti-inflammatory drug (NSAID or COX-2 inhibitor) all at the same time increases the risk of renal impairment (see section 4.4).

### **CYP2C9 inhibitors**

Concomitant administration of ibuprofen with CYP2C9 inhibitors may increase the exposure to ibuprofen (CYP2C9 substrate). In a study with voriconazole and fluconazole (CYP2C9 inhibitors), an increased S(+)-ibuprofen exposure by approximately 80 to 100% has been shown. Reduction of the ibuprofen dose should be considered when potent CYP2C9 inhibitors are administered concomitantly, particularly when high-dose ibuprofen is administered with either voriconazole or fluconazole.

## **4.6 Fertility, pregnancy and lactation Pregnancy**

Fenpaed is contraindicated in third trimester of pregnancy.

Fenpaed should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for NSAID treatment during the first or second trimester, limit use to the lowest effective dose and shortest duration possible.

Data from epidemiological studies suggest an increased risk of miscarriage and congenital malformation associated with NSAID use in early pregnancy.

Use of NSAIDs in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with Fenpaed if oligohydramnios occurs.

NSAID use during the third trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. NSAID use in the third trimester of pregnancy is therefore contraindicated.



### **Use in labour and delivery**

Administration of ibuprofen is not recommended during labor and delivery. The onset of labor may be delayed and the duration increased with a greater bleeding tendency in both mother and child.

### **Breast-feeding**

Ibuprofen is not recommended for use in nursing mothers.

### **Fertility**

The use of ibuprofen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ibuprofen should be considered.

### **4.7 Effects on ability to drive and use machines**

Following treatment with ibuprofen, the reaction time of patients may be affected. Care should be taken when driving or operating machinery as the activity may be affected by dizziness, drowsiness, fatigue and visual disturbance. This applies to a greater extent in combination with alcohol.

### **4.8 Undesirable effects**

#### **Hypersensitivity**

Hypersensitivity reactions have been reported following treatment with ibuprofen. These may consist of (a) non-specific allergic reaction and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and, very rarely, bullous dermatoses (including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

#### **More common reactions (greater than 1%)**

##### ***Gastrointestinal***

The most commonly observed adverse events are gastrointestinal in nature. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis and gastrointestinal haemorrhage and exacerbation of colitis and Crohn's disease have been reported following ibuprofen administration.

##### ***Nervous system disorders***

Headache, dizziness.

##### ***Dermatological***

Rash.

##### ***General disorders and administration site conditions***

Fatigue.

**Less common reactions (less than 1%)**

***Gastrointestinal***

Gastritis, duodenal ulcer, gastric ulcer, mouth ulceration, gastrointestinal perforation, pancreatitis.

***Renal***

Renal nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

***Hepatic***

Abnormal liver function, hepatic failure, hepatitis and jaundice.

***Neurological and special senses***

Visual disturbances, visual impairment, toxic optic neuropathy, optic neuritis, paraesthesia, somnolence, anxiety, depression, insomnia, confusion, hallucinations, tinnitus, hearing impaired, vertigo, malaise, and drowsiness.

***Haematological***

Thrombocytopenia, leucopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

***Immune system disorders***

Hypersensitivity, anaphylactic reaction.

***Dermatological***

Photosensitivity (see 'Hypersensitivity' for other skin reactions).

***General***

Decreased appetite, oedema.

***Cardiovascular***

Cardiac failure, myocardial infarction, stroke.

***Vascular disorder***

Hypertension.

***Respiratory, thoracic and mediastinal disorders***

Asthma, bronchospasm, dyspnea.

***Infections and infestations***

Rhinitis and aseptic meningitis.

## **Not known**

### ***Skin and subcutaneous tissue disorders***

Acute generalised exanthematous pustulosis (AGEP)

Drug reaction with eosinophilia and systemic symptoms (DRESS)

Photosensitivity reactions

## **Post-marketing experience**

### ***Pregnancy, puerperium and perinatal conditions***

Oligohydramnios, neonatal renal impairment

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## **4.9 Overdose**

### **Toxicity**

Signs and symptoms of toxicity have generally not been observed at doses below 100 mg/kg in children or adults. However, supportive care may be needed in some cases. Children have been observed to manifest signs and symptoms of toxicity after ingestion of 400 mg/kg or greater.

### **Symptoms**

Most patients who have ingested significant amounts of ibuprofen will manifest symptoms within 4 to 6 hours.

The most frequently reported symptoms of overdose include nausea, vomiting, abdominal pain, lethargy and drowsiness. Central nervous system (CNS) effects include headache, tinnitus, dizziness, convulsion and loss of consciousness. Nystagmus, metabolic acidosis, hypothermia, renal effects, gastrointestinal bleeding, coma, apnoea and depression of the CNS and respiratory system have also been rarely reported. Cardiovascular toxicity, including hypotension, bradycardia and tachycardia, has been reported. In cases of significant overdose, renal failure and liver damage are possible. Large overdoses are generally well tolerated when no other drugs are being taken.

### **Treatment**

There is no specific antidote for ibuprofen overdose. Gastric emptying followed by supportive measures is recommended if the quantity ingested exceeds 400 mg/kg within the previous hour. For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and Antirheumatic Products, Non-Steroids. ATC code: M01AE01.

Ibuprofen is a colourless crystalline stable solid, with a melting point of 75° to 77°C. It is relatively insoluble in water but readily soluble in most organic solvents.

#### Pharmacodynamic effects

Ibuprofen is a propionic acid derivative nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and anti-pyretic effects. The drug's therapeutic effects are thought to result from its inhibitory effect on the enzyme cyclooxygenase, which results in a marked reduction in prostaglandin synthesis. These properties provide symptomatic relief of inflammation, pain and fever.

#### Clinical efficacy and safety

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred.

Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid/aspirin cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

### 5.2 Pharmacokinetic properties

Ibuprofen is a racemic mixture of [+]S- and [-]R-enantiomers.

#### Absorption

The sustained release form of ibuprofen is formulated to allow a gradual release of the active substance from the gel matrix, with a slower release compared to immediate-release formulations and a lower peak serum concentration which is reached about 3 hours after administration.

Ibuprofen diffuses through an outer gel layer which erodes allowing the aqueous medium to penetrate further into the core. The sustained absorption phase that results provides prolonged plasma levels of ibuprofen in the systemic circulation, reducing the dosage frequency normally required for a drug with a plasma half-life of about two hours.

The mean plasma profile of two sustained release 800 mg tablets compared to one conventional release 400mg tablet taken four times daily, showed that the sustained release formulation reduced the peaks and troughs characteristic of the conventional release tablets and produced higher mean plasma levels at 5, 10 and 15 hours and, notably at 24 hours. The area under the plasma concentration/time curve for two sustained release tablets was almost identical to that of four conventional release 400 mg tablets.

## **Distribution**

Ibuprofen is extensively bound to plasma proteins (99%). Ibuprofen has a small volume of distribution being about 0.12-0.2 L/kg in adults.

## **Biotransformation**

Ibuprofen is rapidly metabolized in the liver through cytochrome P450, preferentially CYP2C9, to two primary inactive metabolites, 2-hydroxyibuprofen and 3-carboxyibuprofen. Following oral ingestion of the drug, slightly less than 90% of an oral dose of ibuprofen can be accounted for in the urine as oxidative metabolites and their glucuronic conjugates. Very little ibuprofen is excreted unchanged in the urine.

## **Elimination**

Excretion by the kidney is both rapid and complete. The elimination half-life of immediate release formulations is approximately two hours. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

## **Special populations**

### *Elderly*

Given that no renal impairment exists, there are only small, clinically insignificant differences in the pharmacokinetic profile and urinary excretion between the young and the elderly.

### *Renal impairment*

For patients with mild renal impairment, increased plasma level of (S)-ibuprofen, higher AUC values for (S)-ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported. In end-stage renal disease patients receiving dialysis, the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis (see sections 4.2, 4.3 and 4.4).

### *Hepatic impairment*

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters.

In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen, an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)- enantiomer (see sections 4.2, 4.3 and 4.4).

## **5.3 Preclinical safety data**

Refer to sections 4.5 and 4.6 for relevant data.

# **6. PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

FENPAED Oral Suspension contains the following inactive ingredients: glycerol (E422), Xanthan Gum,

Maltitol (E965), Polysorbate 80, Saccharin Sodium (E954), Citric Acid Monohydrate, Sodium Methyl Hydroxybenzoate, Sodium Propyl Hydroxybenzoate, purified water and strawberry flavour.

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

48 months.

## **6.4 Special precautions for storage**

Store below 25 °C. Shake bottle well before use.

## **6.5 Nature and contents of container**

Amber glass bottle: 100 mL, 150 mL and 200 mL

HDPE bottle: 500 mL and 1 Litre

Sachets: 5 mL per sachet. Packs of 10 and 20 sachets

## **6.6 Special precautions for disposal**

No special requirements.

# **7. MEDICINE SCHEDULE**

Prescription Medicine: 200 mL, 500 mL and 1 Litre

Pharmacy Only Medicine: 100 mL, 150 mL, 200 mL and sachet pack.

# **8. SPONSOR**

AFT Pharmaceuticals Ltd

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# **9. DATE OF FIRST APPROVAL**

8 July 2004

# **10. DATE OF REVISION OF THE TEXT**

20 December 2022

### Summary table of changes

Date	Section(s) changed	Change(s)
October 2020	4.4, 4.8	Safety update
July 2022	4.6, 4.8	Safety update: alignment of NSAID warnings regarding use in pregnancy
July 2022	6.3	Amendment of text
December 2022	4.4	Safety update: addition of DRESS syndrome
December 2022	4.8	Safety update: addition of photosensitivity reactions
December 2022	All	Minor formatting changes